ICD

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/075,718	02/12/2002	Allan Y. Chen	693243-76 (UCD-1120)	1621

29585 7590 01/27/2005

DLA PIPER RUDNICK GRAY CARY US LLP
153 TOWNSEND STREET
SUITE 800
SAN FRANCISCO, CA 94107-1907

EXAMINER	
KIM, JENNIFER M	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 01/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/075,718	CHEN, ALLAN Y.	
	Examiner	Art Unit	
	Jennifer Kim	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25,27-30,32,33,35,36 and 38-41* is/are pending in the application.

4a) Of the above claim(s) *1-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-25,27-30,32,33,35,36 and 38-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 22, 2004 has been entered.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 23-25, 27-30, 32, 33, 35 and 38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the "treatment of a neoplastic growth associated with lung and breast cancer", does not reasonably provide enablement for the "neoplastic growth associated with tumor or cancer". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

3. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, predictability of the prior art, state of the prior art and the amount of experimentation necessary. All of the **Wands factors** have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: All of the rejected claims are drawn to a method for treating a neoplastic growth associated with tumor or cancer comprising administering indolocarbazole having structure A and radiation. The nature of the invention is extremely complex in that it encompasses the actual treatment of a cell proliferation disorder (i.e. any neoplastic growth associated with any tumor or cancer) such that the subject treated with above combination does not promote a neoplastic growth associated with any tumor or any cancer.

Breath of the Claims: The complex of nature of the claims greatly exacerbated by breath of the claims. The claims encompass a method for treating a neoplastic growth associated with tumor or cancer comprising administering indolocarbazole having structure A and radiation. The neoplastic growth associated with tumor or cancer is a complex cell proliferation disorder in humans, which has potentially many different causes (i.e. many different mutations or combination of mutations). Each of which may or may not be addressed by the administration of the claimed compounds.

Guidance of the Specification: The guidance given by the specification as to how one would administered the claimed compounds to a subject in order to actually treat any neoplastic growth associated with tumor or cancer is minimal. All of the guidance provided by the specification is directed towards treatment of specific neoplastic growth associated with specific tumor or cancer (i.e. lung and breast).

Working Examples: All of the working examples provided by the specification are directed toward the treatment of specific neoplastic growth associated with specific tumor or cancer (i.e. breast, lung) rather than a neoplastic growth associated with any tumor or cancer. The data given by the instant Application to establish the claimed combination would act in the manner claimed as they relate to the actual treatment of any neoplastic growth associated with tumor or cancer in general is minimal. The difficulty in treating pancreatic, liver, colon and skin cancer is clearly known to the art as evidenced by the Carter et al. reference at pages 361 to 365. This illustrates that of approximately 35 drugs tested only 3 showed definite evidence of drug activity in the pancreas and only 4 in the colorectal and colon. Applicants' data has been reviewed but does not establish a correlation between the in-vitro tests performed and the use of applicants active agents in-vivo.

State of the Art: While the state of the art is relatively high with regard to treatment of specific cell proliferation disorders (i.e. breast cancer), the state of the art with regard to treatment of any a neoplastic cell associated with any tumor

or cancer is underdeveloped. In particular, there do not appear to be any examples or teachings in the prior art wherein a compound similar to the claimed compounds was administered to a subject to treat development a neoplastic growth associated with any tumor or any cancer. Further, the difficulty in treating pancreatic, liver, colon and skin cancer is clearly known to the art as evidenced by the Carter et al. reference at pages 361 to 365. This illustrates that of approximately 35 drugs tested only 3 showed definite evidence of drug activity in the pancreas and only 4 in the colorectal and colon.

Predictability of the Art: The lack of significant guidance from the specification or prior art with regard to the actual treatment of a neoplastic growth associated with tumor or cancer comprising the combination of radiation and an indolocarbazole having the structure A in a human subject with the claimed combination makes practicing the claimed invention unpredictable to the extent that the Application is directed to a method for treating any neoplastic growth associated with any tumor or any cancer comprising administering indolocarbazole having structure A and radiation.

The amount of Experimentation Necessary: In order to practice claimed invention, one of skilled in the art would have to first envision a combination of appropriate pharmaceutical carrier, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system for one of the claimed combination and test the combination in the model system to determine whether or not the combination is effective for any neoplastic growth associated

with any tumor or any cancer. If unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regard to treatment of any neoplastic growth associated with any tumor or any cancer with any combination, one of skill in the art would have to then either envision a modification of the first combination of pharmaceutical compound, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above, and test the system again. If again unsuccessful, which is likely given the lack of significant guidance form the specification of prior art regarding treatment of any neoplastic growth associated with any tumor or any cancer with any combination, the entire, unpredictable process would have to be repeated until successful. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to treat any neoplastic growth associated with any tumor or any cancer in a subject by administration of one of combination.

Therefore, a method of treating any neoplastic growth associated with any tumor or any cancer administering the combination comprising indolocarbazole having structure A and radiation is not considered to be enabled by the instant specification.

4. Claims 40 and 41are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the "treatment specific neoplastic growth associated with specific tumor or specific cancer", does not reasonably provide

enablement for the "treatment of **a condition** associated with neoplastic cell". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

5. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, predictability of the prior art, state of the prior art and the amount of experimentation necessary. All of the **Wands factors** have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: All of the rejected claims are drawn to a method for treating a condition associated with neoplastic cell comprising administering indolocarbazole having structure A and radiation. The nature of the invention is extremely complex in that it encompasses the actual treatment of any condition associated with neoplastic cell including cell proliferation disorder (i.e. any condition including any tumor or cancer) such that the subject treated with above combination does not contract any condition associated with neoplastic cell.

Breath of the Claims: The complex of nature of the claims greatly exacerbated by breath of the claims. The claims encompass a condition associated with neoplastic cell comprising administering indolocarbazole having structure A and radiation. The condition associated with neoplastic cell including tumor or cancer is a complex cell proliferation disorder in humans, which has potentially

many different causes (i.e. many different mutations or combination of mutations). Each of which may or may not be addressed by the administration of the claimed combination.

Guidance of the Specification: The guidance given by the specification as to how one would administered the claimed compounds to a subject in order to actually treat any condition associated with neoplastic is minimal. All of the guidance provided by the specification is directed towards treatment of specific condition associated with neoplastic growth (i.e. lung and breast).

Working Examples: All of the working examples provided by the specification are directed toward the treatment of specific condition associated with neoplastic cell involving specific tumor or cancer (i.e. breast, lung) rather than any condition associated with neoplastic cell. The data given by the instant Application to establish the claimed combination would act in the manner claimed as they relate to the actual treatment of any condition associated with neoplastic cell in general is minimal. The difficulty in treating pancreatic, liver, colon and skin cancer is clearly known to the art as evidenced by the Carter et al. reference at pages 361 to 367. This illustrates that of approximately 35 drugs tested only 3 showed definite evidence of drug activity in the pancreas and only 4 in the colorectal and colon. Applicants' data has been reviewed but does not establish a correlation between the in-vitro tests performed and the use of applicants active agents in-vivo.

State of the Art: While the state of the art is relatively high with regard to treatment of specific condition related to cell proliferation disorders (i.e. breast cancer), the state of the art with regard to treatment of any condition associated with neoplastic cell is underdeveloped. In particular, there do not appear to be any examples or teachings in the prior art wherein a combination similar to the claimed combination was administered to a subject to treat development of any condition associated with neoplastic cell.

Predictability of the Art: The lack of significant guidance from the specification or prior art with regard to the actual treatment of a condition associated with neoplastic cell associated with tumor or cancer comprising the combination of radiation and an indolocarbazole having the structure A in a human subject with the claimed combination makes practicing the claimed invention unpredictable to the extent that the Application is directed to a method for treating any condition associated with neoplastic cell comprising administering indolocarbazole having structure A and radiation.

The amount of Experimentation Necessary: In order to practice claimed invention, one of skilled in the art would have to first envision a combination of appropriate pharmaceutical carrier, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system for one of the claimed combination and test the combination in the model system to determine whether or not the combination is effective for any condition associated with neoplastic cell including any tumor or any cancer. If unsuccessful, which is likely

given the lack of significant guidance from the specification or prior art regard to treatment of any condition associated with neoplastic cell including any tumor or any cancer with any combination, one of skill in the art would have to then either envision a modification of the first combination of pharmaceutical combination, combination dosage, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above, and test the system again. If again unsuccessful, which is likely given the lack of significant guidance form the specification of prior art regarding treatment of any condition associated with neoplastic cell including any tumor or any cancer with any combination, the entire, unpredictable process would have to be repeated until successful. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to treat any condition associated with neoplastic cell in a subject by administration of one of combination.

Therefore, a method of treating any condition associated with neoplastic cell administering the combination comprising indolocarbazole having structure A and radiation is not considered to be enabled by the instant specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 23-25, 27-30, 32, 33, 35, 36 and 38-41are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (1997) in view of Prudhomme (2000).

Chen et al. teach that the role of DNA topoisomerase I as a biochemical mediator of radiosensitization in cultured mammalian cells by camptothecin derivatives and it was found that camptothecin enhanced the cytotoxicity of radiation in a schedule-dependent manner by interaction with DNA topoisomerase I. Chen et al. also teach that DNA topoisomerase I, the major cytotoxic target of camptothecin derivatives, was proposed to play a pivotal role in inducing radiosensitization in cells. Chen et al. also demonstrated that mammalian DNA topoisomerase I mediated the enhancement of radiation cytotoxicity. Chen et al. suggest a potential development of topoisomerase I drugs as radiosensitizer in treating human malignancies. Chen et al. teach that the combination of chemotherapy and radiation therapy has become the treatment of choice for a number of advanced human malignancies. Chen et al. teach that a number of

chemotherapeutic drugs are known to be able to synergistically enhance the cytotoxicity of ionizing radiation.

Prudhomme teaches that rebeccamycin analogues are an antitumor agent and they inhibit the activity of topoisomerase. Prudhomme teaches that rebeccamycin analogues exhibit potent inhibitory potencies against topoisomerase I. Prudhomme teaches rebeccamycin analogues have an antitumor activity agonist gastric, colorectal breast, liver and lung cancer. (table 10).

The primary reference does not teach the rebeccamycin analogues in combination with radiation.

It would have been obvious to one of ordinary skill in the art to replace rebeccamycin analogues in place of camptothecin because that rebeccamycin analogues are antitumor agent and they too inhibit the activity of topoisomerase like camptothecin. One of ordinary skill in the art would have been motivated to make such a modification with reasonable expectation of success to provide enhanced cytotoxicity of radiation in with rebeccamycin analogue posing same mechanism as camptothecin (i.e. topoisomerase I inhibition), which is pivotal in enhancement of radiation cytotoxicity. Absent any evidence to contrary, there would have been reasonable expectation of successfully treating neoplastic growth comprising administration of rebeccamycin and radiation since the combination of chemotherapy and radiation therapy has become the treatment of choice for a number of advanced human malignancies and a number of chemotherapeutic drugs are known to be able to synergistically enhance the cytotoxicity of ionizing radiation as taught by Chen et al. Further, there is a suggestion of a

potential development of topoisomerase I drugs as radiosensitizer in treating human malignancies by Chen et al. It is noted that rebeccamycin analogue and radiation therapy have common utility of having antitumor activity. One of ordinary skill in the art would have been motivated to employ a potent topoisomerase I drug such as rebeccamycin with radiation in treating human malignancies in a method taught by Chen et al. The amounts of active agents to be used at a noncytotoxic level is obvious because the combination of topoisomerase inhibitor I and radiation treatment provided enhanced cytotoxicity effect as taught by Chen et al. One of ordinary skill in the art would be motivated to use reduced amounts of the active agent to avoid unnecessary extra dosage of potent chemotherapeutic agents. For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 103.

None of the claims are allowed.

Response to Arguments

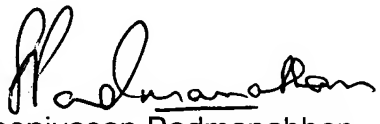
Applicant's arguments filed October 22, 2004 have been fully considered but they are not persuasive. Applicant argues that the specification lists several example of neoplastic growth including prostate cancer, bone tumor, colon cancer, lymphoma and brain tumor and in addition, the specification provides examples to demonstrate the efficacy of the present invention in different types of cells. This is not persuasive

because all of the working examples provided by the specification are directed toward the treatment of specific condition associated with neoplastic cell involving specific tumor or cancer (i.e. breast, lung) rather than any condition associated with neoplastic cell. To the extent that the Application is directed to a method of treating a neoplastic growth of any tumor or any cancer cell in vivo, which is highly speculative, a greater amount of evidence is required to show its operability in humans to treat any neoplastic growth associated with any tumor or cancer. The data given by the instant Application to establish the claimed combination would act in the manner claimed as they relate to the actual treatment of any condition associated with neoplastic cell in general is minimal. Applicant's data has been reviewed but does not establish a correlation between the in-vitro tests performed and the use of applicant's active agents in-vivo for any neoplastic growth associated with any tumor or any cancer. Applicant next argues that the methods provided by the present invention use indolocarbazole derivatives at a non-cytotoxic level to enhance the radiosensitivity of cells, but not to produce cytotoxic effect. This is not persuasive because rebeccamycin analogues are an antitumor agent and they have an antitumor activity against gastric, colorectal, breast liver and lung cancer as taught by Prudhomme. Prudhomme still applies since it too obviously is does not cause a substantial cytotoxic effect since same rebeccamycin analogues prior art possess same property as claimed by Applicant. Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Kim whose telephone number is 571-272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Sreenivasan Padmanabhan
Supervisory Examiner
Art Unit 1617

Jmk
January 11, 2005